REMARKS

This is in response to the Office Action mailed December 18, 2002, in the above-referenced application. The rejections of record are addressed below in the order presented in the Office Action.

Claims 5, 10, 24 and 25 are rejected under 35 USC § 112, second paragraph, as indefinite. Claims 5, 10, 24 and 25 have been amended to delete the phrase "for example" or "such as." In addition, dependent Claims 33, 34, 35, 36, 37, 38, and 39 are added to recite the embodiments exemplified by the objected to phrases in Claims 5, 10, 24 and 25. Applicants accordingly respectfully request withdrawal of this rejection.

Claims 6-8, 10-12, 22, 24, 25 and 32 are rejected under 35 USC § 102(b) as anticipated by Randen et al. Applicants respectfully traverse this rejection.

By way of background, the present invention is directed to water soluble particles and methods of making the same. The particles include a coprecipitant core with a dehydrated biological macromolecule coating thereon. In contrast, as discussed in more detail below, the art relied by the Office in the rejections of record is directed to particles that contain occluded or entrapped protein, i.e., particles in which the protein is distributed throughout a polymer matrix.

In the method of the invention, an aqueous solution of the coprecipitant and the biological macromolecule is prepared and rapidly admixed with an excess of a water miscible organic solvent. The coprecipitant and bioactive molecule immediately coprecipitate from the solution to form the particles.

Advantageously, the coprecipitant is a non-polymeric material, such as exemplified at page 6, lines 10-22, of the application. One skilled in the art would recognize that several of the noted coprecipitants are not polymeric materials. New dependent Claims 40 and 41 are added to present this aspect of the invention for consideration by the Examiner. Claims 40 and 41 do not add new matter but merely exemplify a group of coprecipitants represented by the numerous compounds listed on page 6 of the application.

The use of a non-polymeric coprecipitant is contrary to the teachings of the art, as also discussed in more detail below. In contrast to this aspect of the invention, the art suggests that a

polymer coprecipitant is required to stabilize the protein by entrapping it within a polymer matrix.

The art also teaches away from the use of low molecular weight polymer coprecipitants, such as low molecular weight polymers less than 10,000 Da as recited in Claims 5, 10, 24, 25, 28 and 29. In contrast to the claimed invention, the art suggests higher molecular weight polymers are required to form the polymer matrix. The art indicates that a low molecular weight polymer would not work because the low molecular weight polymer cannot wrap around a protein in the same way that a high molecular weight polymer can.

Turning now to the Randen et al., this article does not teach the claimed invention. Randen et al. describe the precipitation of enzymes with starch. The art when considered as a whole indicates that precipitation is carried out by adding the same volume of solvent to the aqueous phase. See Bustos et al., J. Chem. Tech. Biotechnol., 1996, pages 193-199, cited by Applicants.

In contrast, the present inventors have found that commercial applications require controlled addition of aqueous solution to an excess of solvent. If this protocol is not followed the difficulty of rapidly mixing large volumes means that there is a risk that the process will be too slow and as a result, the protein precipitates separately from the microcrystals. See Example 5 in the present application. The unexpected benefit of adding the aqueous solution to the solvent in a controlled manner as claimed is not described in Randen et al.

The claimed invention differs in other respects as well. Randen et al. is directed specifically to the formation of starch based particles. Randen et al. nowhere suggests that other materials may be used for coprecipitation.

Further, the Randen et al. article suggests if anything that the process works only with polymers. See page 765, the paragraph under the heading "Discussion." Here Randen et al. state that occlusion is the likely mechanism occurring during the process. Randen et al. goes on to state on page 765, column 2, fourth full paragraph, that:

"The use of coprecipitation with starch reduces the denaturation of the protein by physically entrapping of the enzyme into the support matrix thereby protecting the enzyme from the denaturing environment" (emphasis added).

Page 765, column 2, first full paragraph, states:

"This stabilization is probably attributable to the interaction of enzyme molecules with the starch support. In principle, protein molecules can form hydrogen bonds with hydroxy groups of the support."

Since protein molecules are large, entrapment or occlusion of the protein molecules within a matrix made by coprecipitating materials other than polymers would be expected to be extremely difficult.

In addition, on page 765, second column, second full paragraph, Randen et al. state:

"This precipitation step also seemed to effect further purification of the enzyme extract which is reflected in an increase in this specific activity."

This suggests that low molecular weight compounds are not precipitated together with the starch. Accordingly, Randen et al. teaches away from the use of low molecular weight compounds as useful coprecipitants.

As a result the resultant particles produced in accordance with Randen et al. differ structurally from the claimed particles. The Randen et al. process results in a polymer matrix entrapping the enzyme within the same. In contrast, as recited in Claim 6, the claimed process results in a coprecipitant core with a dehydrated biological macromolecule coated thereon.

In summary, the claimed invention differs significantly in several aspects from Randen et al. Randen et al. do not teach controlled addition of an aqueous solution to the solvent, nor the use of an excess of the solvent. Further, the Randen et al. article does not teach use of a non-polymeric coprecipitant. In addition, using high molecular weight starch as taught in Randen et

al. results in the production of particles containing occluded or entrapped protein, i.e., particles in which the protein is distributed throughout a polymer matrix. In contrast, the claimed invention is directed to a method of making particles including a coprecipitant core with a dehydrated biological macromolecule coated thereon. Accordingly, Applicants submit that the claimed invention is not anticipated by Randen et al. and request withdrawal of this rejection.

Claims 1-12, 20-25, 27 and 32 are rejected under 35 USC § 103 as unpatentable over Randen et al. Applicants respectfully traverse this rejection as well.

The differences between the claimed invention and Randen et al. are discussed above. The Office acknowledges that Randen et al. is silent with regard to the teaching of particles having a size of less than 50 micrometers. However, the Office argues that Randen et al. teach milling or grinding particles. Applicants respectfully submit, however, that Randen et al. in fact teach that milling is not generally applicable to such systems.

The Office's attention is directed to page 764, column 1, paragraph 4, which states:

> "The precipitate containing LMM starch was more difficult to mill owing to adhesion to the surface of the mill and also to formation of large agglomerates. Milling therefore appears not to be possible because of the adhesion to the mill."

Table 3 on page 764 illustrates that only 1% of the particles obtained following milling of the aggregates of high molecular mass starch were less than 45 microns.

It is well known in the art that high energy milling of protein-containing particles generally leads to denaturation. Higher energy milling would be required to reduce the average "milled" size from 180 to 380 microns as set forth in Randen et al. to below 50 microns. It is therefore apparent that milling may not be generally applied to these systems and is coprecipitant dependent as lower molecular weight coprecipitants may not necessarily be milled. Furthermore, it is clear from the data in Table 3 that the size range expected following milling is in the range of 90 to 500 microns. Still further, milling is unlikely to be useful to obtain significantly smaller particles because high energy systems are required, which systems are known to denature by a

molecule. Accordingly, Applicants submit that the claimed invention is not obvious in view of Randen et al. and request withdrawal of this rejection as well.

Claims 22 and 32 are rejected under 35 USC § 103 as unpatentable over Novo WO 97/34919. Applicants respectfully traverse this rejection as well.

The Novo publication is directed to a method of obtaining protein crystals. Protein crystals are quite different from the product of the present invention. Protein crystals consist of an ordered 3-dimensional lattice of protein molecules that are repeated throughout the crystal/particles. The core of a protein crystal is protein; the surface of the crystal is the same protein.

Within the protein crystal there will be entrapped solvent, salt and counterions but these do not form a support and can generally be exchanged without losing the structure. Indeed, in many cases, additives such as salts and organic solvents are added to the protein solution to the reduce the solubility of the protein and encourage the onset of crystallization. While such reagents are sometimes collectively referred to a "coprecipitants," they are not expected to coprecipitate with the protein because the aim is to obtain pure protein crystals.

If too much organic solvent is added to the protein solution, the salts may also sometimes precipitate as crystals. However, these crystals are pure salt crystals and not coated with protein. Also, such salt crystals are generally larger than 50 microns.

Accordingly, the skilled artisan would conclude from the Novo publication that coprecipitation of a salt and a protein by addition of a solvent would lead to a separate precipitation of salt crystals and particles or crystals containing pure protein. This is demonstrated in the present application in Example 5 and Figure 5.

In summary, the Novo publication is directed to a different process to produce a different product than that claimed. The differences in the resultant composition are significant in that Novo results in protein crystals and the claimed invention in a particle with a coprecipitant core coated with the protein. In view of the foregoing, Applicants respectfully request withdrawal of this rejection as well.

Claims 1-5, 13-21, 23 and 26-31 are rejected under 35 USC § 103 as unpatentable over U.S. Patent No. 5,198,353 to Hawkins et al. and EP 356,239 to Langley et al. Applicants respectfully traverse this rejection as well.

Hawkins et al. is directed to the production of particles which are initially produced with the protein in a hydrated state. The particles are dried in Hawkins et al. by a separate spray drying step. See Example 5. Further, the process of Hawkins et al. is applied to polymers only with no mention of the possibility of using non-polymeric coprecipitants.

The Office acknowledges that Hawkins is silent with regard to particles of a size less than 50 μm. While the Examiner relies upon Langley et al. to support the position that it would have been obvious to modify the Hawkins process to obtain particles having a size of less than 20 μm.

The process used in Langley et al., however, is very different from that used in Hawkins et al. The process in Langley et al. relates to an emulsification step that requires an amphipathic polymeric stabilizer. This stabilizer must be able to interact with both the polymer and the non-polar organic solvent phase. The choice of polymers that can be applied is thus restricted to those that can interact with the stabilizer.

The only polymer exemplified by Langley et al. is the ionic polymer ammonium polyacrylate, which has a molecular weight of 30,000 (see Example 1). The low molecular weight non-ionic polyvinyl alcohol and polyvinyl pyrrolidone polymers of Hawkins et al. accordingly would be unsuitable for use in the Langley et al. process. In addition, the resultant particles produced by the Langley et al. process have enzyme distributed throughout a polymer matrix.

Accordingly, there is no motivation to combine the references as suggested by the Office. Even if the references were combined, the result would not be the same as that claimed, namely, particles having a coprecipitant core and a protein coating thereon. Rather, the result would be particles with the enzyme distributed throughout a polymer matrix.

In summary, all of the references relied upon by the Office relate to methods of coprecipitating polymers and proteins to make particles in which the protein is distributed throughout a polymer matrix. In contrast, the present invention is directed to particles including a coprecipitant core coated with the protein. Thus, the claimed invention is directed to a very

different end product than that of the cited art. The claimed invention also differs from the art because the coprecipitant is non-polymeric or a polymer having a low molecular weight. In contrast, the cited art is directed to processes in which a high molecular weight polymer is the corprecipitant. Indeed, when considered as a whole, the art teaches away from the claimed invention, suggesting that high molecular weight coprecipitants are required to provide a sufficient matrix through which the protein is distributed.

The rejections of record having been addressed in full in the foregoing, Applicants respectfully submit that this application is now in condition for allowance, which action is respectfully solicited. Should the Examiner have any questions regarding the foregoing, it is respectfully requested that she contact the undersigned at her convenience.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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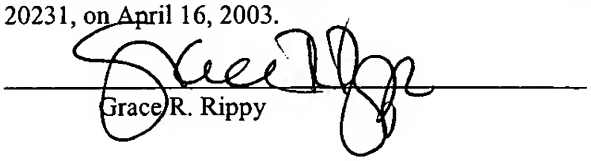

Grace R. Rippy

Version with Markings to Show Changes Made:

5. (Amended) Water soluble particles according to claim 1 wherein the coprecipitant is selected from inorganic salts,
sugars, polysaccharides, carbohydrates, polyols, and derivatives thereof[, for example trehalose,] with a molecular weight of less than 10,000 Da;
amino-acids [such as glycine and arginine];
acid-base buffers;
zwitterionic compounds;
organic salts;
compounds containing multiple basic groups;
compounds containing multiple acidic groups;
bile salts;
water soluble dyes;
polar or ionic polymers; and
polar or ionic dendrimers.

10. (Amended) The method according to claim 6 wherein the coprecipitant is selected from
inorganic salts,
sugars, polysaccharides, carbohydrates, polyols, and derivatives thereof[, for example trehalose,] with a molecular weight of less than 10,000 Da;
amino-acids;
acid-base buffers;
zwitterionic compounds;
organic salts;
compounds containing multiple basic groups;
compounds containing multiple acidic groups;
bile salts;

water soluble dyes;
polar or ionic polymers; and
polar or ionic dendrimers.

24. (Amended) Biological macromolecule coated micro-crystals comprising a coprecipitant core with a dehydrated biological macromolecule coated thereon wherein the coprecipitant is selected from inorganic salts,
sugars, polysaccharides, carbohydrates, polyols, and derivatives thereof[, for example trehalose,] with a molecular weight of less than 10,000 Da;
amino-acids [such as glycine and arginine];
acid-base buffers;
zwitterionic compounds;
organic salts;
compounds containing multiple basic groups;
compounds containing multiple acidic groups;
bile salts;
water soluble dyes;
polar or ionic polymers; and
polar or ionic dendrimers.

25. (Amended) A pharmaceutical formulation comprising biological macromolecule coated micro-crystals comprising a coprecipitant [cover] core with a dehydrated pharmaceutically active biological macromolecule coated thereon wherein the coprecipitant is selected from inorganic salts,
sugars, polysaccharides, carbohydrates, polyols, and derivatives thereof[, for example trehalose,] with a molecular weight of less than 10,000 Da;
amino-acids [such as glycine and arginine];
acid-base buffers;
zwitterionic compounds;

organic salts;

compounds containing multiple basic groups;

compounds containing multiple acidic groups;

bile salts;

water soluble dyes;

polar or ionic polymers; and

polar or ionic dendrimers; and a suitable carrier therefore.